HUNTER AND FORAGER

Medical schools equip future doctors with some of the information they will need to practice effectively. The traditional curriculum does not ensure that they become informed consumers of medical information who are capable of finding, evaluating, and applying new information as it becomes available. To be lifelong learners, doctors have to rely on new methods of learning while caring for patients, by using tools that help them to hunt and forage through the jungle of information.

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Pharmacogenomics

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We all differ in our response to drug treatment—occasionally with dramatic effects. The era of "one drug fits all patients" is about to give way to individualized therapy matching the patient's unique genetic make up with an optimally effective drug.[1] Pharmacogenetics and pharmacogenomics are the emerging disciplines that are leading the way towards individualized medicine.[2,3] Initially, researchers focused their attention on pharmacogenetics—variations in single candidate genes responsible for variable drug response. Subsequently, studies involving the entire human genome broadened the scope of investigation, giving rise to pharmacogenomics as one of the "hottest" fields in biotechnology today.

Summary points

- Response to drug treatment can vary greatly between patients; genetic factors have a major role in treatment outcome
- Pharmacogenetics and pharmacogenomics are emerging disciplines that focus on genetic determinants of drug response at the levels of single genes or the entire human genome respectively
- Technologies involving gene chip arrays can determine thousands of variations in DNA sequences for individual patients; most variants are single nucleotide polymorphisms
- Pharmacogenomics aims at establishing a signature of DNA sequence variants that are characteristic of individual patients to assess disease susceptibility and select the optimal drug treatment
- This approach has the potential to revolutionize prevention and treatment of diseases

PHARMACOGENETICS

Unexpected drug reactions have been noted for some time, but the systematic study of hereditary origins began only in the 1950s. A few patients developed prolonged

respiratory muscular paralysis after being given succinylcholine, a short acting muscle relaxant widely used in surgery and electroshock treatment. In the 1970s, a trial with the antihypertensive agent debrisoquin resulted in a precipitous drop of blood pressure and collapse in nearly 10% of volunteers. Furthermore, isoniazid therapy for tuberculosis caused peripheral neuropathies in patients who were sensitive to the neurotoxic effects of the drug. Ground breaking genetic and biochemical studies by Werner Kalow and others showed that these adverse effects result from polymorphisms in genes encoding the drug metabolizing enzymes serum cholinesterase, [4] cytochrome P-450, [5] and N-acetyltransferase. [6] These observations laid the foundation for pharmacogenetics.

Functional analysis

Today, many examples of genetic variability in drug response and toxicity are known (Table 1). In a few cases, genetic tests are beginning to find their way into clinical practice. In cancer chemotherapy with thioguanine, severe toxicity or even death can result if a patient is unable to inactivate the drug. Functional assays of thiopurine methyltransferase in red blood cells or genotyping can identify those patients who are at risk and must be given a much lower dose of thioguanine.[7,8] This is particularly critical for the 1 in 300 patients who is homozygous for null alleles (non-functional) of the gene encoding thiopurine methyltransferase which converts the drug to its inactive methylated form. Therefore, genotyping or functional

Table 1 Examples of inherited or acquired variations in enzymes and receptors that affect the drug response[23]

Protein	Phenotype	Drugs	Modified response
Enzymes			
Plasma pseudocholinesterase	Slow hydrolysis of certain esters	Succinylcholine	Prolonged apnea
N-acetyltransferase	Slow, rapid acetylators	Isoniazid	Slow: toxic neuritis, lupus erythematosus
		Procainamide	Disease susceptibility
		Dapsone	Slow: bladder cancer
		Sulfadimidine, sulfasalazine, p-aminosalicylic acid, heterocyclic amines (foot mutagens)	Rapid: colorectal cancer
Thiopurine methyltransferase	Poor thiopurine methyltransferase methylators	6-mercaptopurine, 6-thioguanine, azathioprin	Bone marrow toxicity, liver damage
Dihydropyrimidine dehydrogenase	Slow inactivation	5-fluorouracil	Possible enhanced toxicity
Aldehyde dehydrogenase	Fast, slow metabolizers	Ethanol	Slow: facial flushing Fast: protected from liver cirrhosis
Catechol O-methyl transferase	High, low methylators	Levodopa, methyldopa	Low: increased response
Cytochrome P-450 subtype CYP 2D6	Ultrarapid*	Debrisoquin Sparteine	Poor: increased toxicity
	Extensive*	Phenformin	Extensive: lung cancer?
	Poor metabolizers	Nortriptyline, dextromethorphan, etc	Rapid: drug resistance
Cytochrome P-450 subtype CYP 2C19	Poor, extensive hydroxylators	Methoin, hexobarbitone, omeprazol, proguanil, etc	Poor: increased toxicity; ineffectiveness (proguanil)
Receptors			
β_2 adrenoceptor	Enhanced downregulation	Salbutamol	Poor control of gasping, wheezing in asthma
5-HT2A serotonergic receptor	Various polymorphisms	Clozapine	Associated with variable efficacy
HER2	Overexpression in breast and other cancers	Trastuzumab (Herceptin)	Overexpression associated with therapeutic efficacy
Transporters			
Multiple drug resistance transporter	Overexpression in cancer	Vinblastin, doxorubicin, paclitaxel, etc	Drug resistance

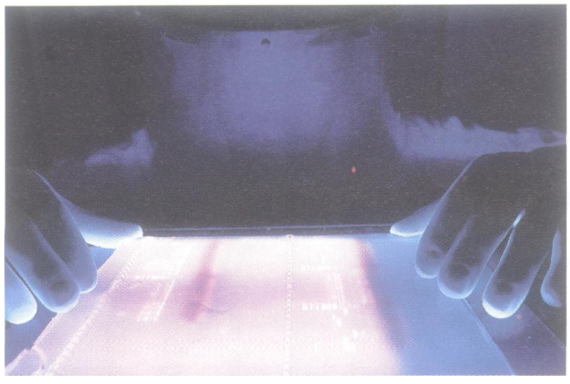
*Hyperactivity can result from activating mutations or gene duplications.

analysis has become standard practice in major cancer treatment centers such as the Mayo Clinic in Rochester and St Jude Children's Research Hospital in Memphis.

Cytochrome P-450

The large family of cytochrome P-450 genes has been most intensely studied because it contains the main drug metabolizing enzymes encoded by numerous genes.[2] Among the cytochrome P-450 subtypes, CYP2D6 and CYP2C19 play a critical part in determining the response to several drugs. This is particularly important for lipophilic drugs—such as drugs that act on the central nervous system and penetrate the lipophilic blood-brain barrier—because renal excretion is minimal and cytochrome P-450 metabolism provides the only means of effective drug elimination. Thus, homozygous carriers of CYP2D6 null alleles and cannot readily degrade and excrete many drugs, including debrisoquin, metoprolol, nortriptyline, and propafenone.[9] These patients are termed "poor metabolizers" for CYP2D6 selective drugs. Because of this they are exquisitely sensitive to these drugs. The incidence of "poor metabolizers" varies greatly among ethnic groups, ranging from 1% in Japanese to 15% in Nigerians. Similarly, patients with defective CYP2C19 subtypes are highly sensitive to methoin, hexobarbital (hexobarbitone), and other drugs selectively metabolized by this P-450 isoform.

The principal molecular defect in poor metabolizers is a single base pair mutation (A→ΠG) in exon 5 of CYP2C19.[10] Gene chips designed to test for polymorphisms of the main subtypes of cytochrome P-450 are now commercially available, but not yet in general clinical use. Cytochrome P-450 polymorphisms also affect the inactivation or, in some cases, activation or toxification of xenobiotics, and thus affect an individual's susceptibility to environmental toxins. This is studied in a field of research called toxicogenetics. Launched recently by the US National Institute of Environmental Health Sciences, the environmental genome project aims at understanding genetic factors in individual responses to the environment and parallels the study of genetic variability in drug response.[11]



VolkerSteger/SPL

Drugs will be fitted to genotypes

PHARMACOGENOMICS

As a scientific discipline, pharmacogenetics has made steady progress, but the human genome project has shattered any complacency as it has revealed profound gaps in our knowledge. By broadening the search for genetic polymorphisms that determine drug responses, the new field of pharmacogenomics begins to supersede the candidate gene approach typical of earlier pharmacogenetic studies. Initially hailed by pharmaceutical biotechnology as the latest trend in biotechnology, pharmacogenomics is now taken seriously everywhere. While genomic techniques serve to identify new gene targets for drug research, and some might refer to this as pharmacogenomics, the broader consensus is that pharmacogenomics deals specifically with genetic variability in drug response. The distinction between pharmacogenetics and pharmacogenomics remains blurred, but here are some of the new ideas typical of pharmacogenomics.

Searching for responsible genes

Each drug is likely to interact in the body with numerous proteins, such as carrier proteins, transporters, metabolizing enzymes, and multiple types of receptors.[1] These proteins determine the absorption, distribution, excretion, targeting to the site of action, and pharmacological response of drugs. As a result, multiple polymorphisms in many genes could affect the drug response, requiring a genome-wide search for the responsible genes. We now know that that there are thousands of receptor genes in the human genome, many of which are closely related to each other because they have evolved by gene duplications. Therefore, we must anticipate that a drug rarely binds just to a single receptor but rather interacts promiscuously with several receptor types. Chlorpromazine, for example, is known to engage several dopaminergic, adrenergic, and serotonergic receptors. As a result, polymorphisms in multiple genes can affect the drug response.

Polymorphisms

Polymorphisms are generally defined as variations of DNA sequence that are present in more than 1% of the population. Most polymorphisms are single nucleotide pòlymorphisms (referred to as "snips"). As the human genome contains three billion nucleotides, and variations between individuals occur in ~1/300 base pairs, around10 million single nucleotide polymorphisms probably exist. Only 1% of these may have any functional consequence at

all, and thus individuals differ from each other genetically by roughly 100,000 polymorphic sites, providing for near infinite variety. As only a small fraction of these single nucleotide polymorphisms will prove relevant to drug response, our goal will be to identify the most important variants.

Microarray gene chips

Novel technology in the form of microarray chips enables us to scan the entire human genome for relevant polymorphisms.[12,13] We can determine simultaneously many thousands of polymorphisms in a patient. At present, these single nucleotide polymorphisms are selected merely as markers evenly distributed throughout the genome, in the hope that functionally relevant polymorphisms can be associated with specific markers by virtue of their proximity on the chromosome. Such genome-wide association studies are already being used in the discovery of susceptibility genes for diseases such as asthma and prostrate cancer, but they are equally suitable for determining the genes involved in drug response. Genome-wide scanning can identify these genes even if we do not know the mechanisms by which the drug acts in the body. The French genomics company, Genset, currently uses gene chips with 60,000 single nucleotide polymorphism markers—sufficient for a complete genomic scan—applied to clinical drug trials in partnership with major pharmaceutical companies. Expanding the number of single nucleotide polymorphisms and selecting functionally relevant single nucleotide polymorphisms in coding or promoter/enhancer regions of genes is quite feasible with current technology and would greatly enhance the power of genome-wide scanning. Herein lies the main incentive for the current rush in the pharmaceutical industry to patent single nucleotide polymorphism markers. It might also be possible to salvage useful experimental drugs that would have failed with standard clinical trials, because of an unacceptable incidence of toxicity in a poorly defined patient population. Stratifying patient populations in relation to genetic criteria emerges as a major challenge to the pharmaceutical industry. Undoubtedly, the insights expected to emerge from such an approach are staggering, but they cannot be gauged accurately at present.

Chip technology

Microarrays can further serve to determine the expression pattern of genes in a target tissue. This shows the mechanisms of drug action in a genomic context. It can also clarify interindividual differences in drug response that are downstream of immediate drug effects in the body by shear force of the massive amount of information emanating from chip technology. Analyzing the entire transcriptional program of a tissue, for example fibroblasts in response to serum stimulation,[14] provides unprecedented details of a complex system and leads to new insights in pathophysiology and biological drug response. Tissue transcript profiling is especially appropriate in cancers because mRNA can be extracted from biopsy specimens or surgical samples. Altered gene expression in the tumor can serve as a guide for selecting effective drug therapy or avoiding unnecessary exposure to toxic but ineffective drugs—for example the overexpression of drug resistance genes encoding transporters (Table 1).

PROMISE OF PHARMACOGENOMICS

These advances are the harbinger of profound changes in treatment. What then do we expect to gain from pharmacogenomics? In the near future, genotyping can help avert severe drug toxicity that is genetically determined but occurs only rarely. Alternatively, drugs may be designed a priori so that they are not subject to extreme variations that result from a few well defined polymorphisms. Drug structures under development are already being selected so that they do not interact with cytochrome P-450 subtype CYP2D6 to avoid unwarranted toxicity in people who metabolize this poorly.

Predicting drug efficacy

Looking farther ahead, and on a much broader scale, we could improve drug efficacy by distinguishing between people who respond well to a drug and those who respond poorly. Often, an effective drug response is found in a few patients treated, while most benefit little or not at all. Much could be gained if we could select the optimal drug for the individual patient before treatment begins. Perhaps a gene chip that establishes a single nucleotide polymorphism signature involving multiple genes relevant to therapeutic outcome for each individual will be developed. This signature could offer insights into an individual's susceptibility to disease and responsiveness to drugs, enabling optimal drug selection by genetic criteria. For example, cure rates with combined surgical and drug treatment of advanced colorectal carcinoma range from 20% to 40%, while the remainder of the patients experience little gain or even severe toxicity from chemotherapy. If we could predict which patients respond best to a particular drug—or better, which drug will yield optimal effects for a given patient—much will be gained. The success of this approach will depend critically on the selection of single nucleotide polymorphisms tested by the gene chip. Single nucleotide polymorphisms must be informative and many must be tested to scan the entire genome. This task is by

no means complete and constitutes a major goal of those companies which are focusing on genomics.

LIMITATIONS

There are also formidable obstacles that we are unlikely to overcome in the near future. The dynamic complexity of the human genome, involvement of multiple genes in drug responses, and racial differences in the prevalence of gene variants impede effective genome-wide scanning and progress towards practical clinical applications. Furthermore, the drug response is probably affected by multiple genes, each gene with multiple polymorphisms distributed in the general population. For example, the anticancer drug 5-fluorouracil used in the treatment of colorectal cancer is activated and inactivated by nearly 40 different enzymes. Each of these is currently being scanned for relevant polymorphisms at the biotech company Variagenics. Dihydropyrimidine dehydrogenase is a likely candidate in 5-fluorouracil inactivation (Table 1). However, whether extensive genotyping will provide useful predictors of clinical response remains to be seen.

Racial differences add further confounding factors. Drug response might be predicted from a certain pattern of polymorphisms rather than only a single polymorphism, yet these patterns probably differ between ethnic groups. This could prevent us from making predictions about drug responses across the general patient population, and it emphasizes the need to stratify clinical pharmacogenomic studies.

Genomic technologies are still evolving rapidly, at an exponential pace similar to the development of computer technology over the past 20 years. We are not certain where genomic technologies will be 10 years from now.

Ethical issues also need to be resolved. Holding sensitive information on someone's genetic make up raises questions of privacy and security and ethical dilemmas in disease prognosis and treatment choices. After all, polymorphisms relevant to drug response may overlap with disease susceptibility, and divulging such information could jeopardize an individual. On the other hand, legal issues may force the inclusion of pharmacogenomics into clinical practice. Once the genetic component of a severe adverse drug effect is documented, doctors may be obliged to order the genetic test to avoid malpractice litigation.

IMPACT OF PHARMACOGENOMICS

Pharmacogenomics will have profound impact on the way drug treatment is conducted. We can include here bioengineered proteins as drugs, or even gene therapy designed to deliver proteins to target tissues. These treatments are also subject to constraints and complexities engendered by individual variability. A case in point is the treatment of breast cancer with trastuzumab (Herceptin; Genentech, USA) a humanized monoclonal antibody against the HER2 receptor. Overexpression of HER2 may occur as a somatic genetic change in breast cancer and other tumors. This correlates with poor clinical prognosis and serves as a marker for effective therapy with trastuzumab, either alone or in combination with chemotherapy.[15,16]

Whether we will see broad use of gene chips in clinical use within 10 years is questionable, but the mere knowledge of the principles underlying genetic variability will prove valuable in optimizing drug therapy. Pharmacogenomics will lead us towards individualized therapy, but it will also help us understand limitations inherent in treating disease in a broad patient population

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